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PATENT 82419.0003
Express Mail Label No. EL589806672

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Anticipated Classification
of this Application:
☒ Class 422 ☒ Subclass 028.000
Prior Application 09/130,542
Examiner: E. McCane
Art Unit: 1744

CONTINUATION APPLICATION TRANSMITTAL

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is a request for filing a new continuation application pursuant to 37 C.F.R. § 1.53(b), of pending prior application:

Serial No. 09/130,542 filed August 6, 1998, by Chris De Bruijn, F. Richard Christ, Anthony J. Dziabo, Joseph Vigh (inventors currently of record in prior application) for CONTACT LENS AND OPHTHALMIC SOLUTIONS.

1. ☒ Enclosed is a copy of the prior application, including the oath or declaration as originally filed, or a replacement specification which does not add new matter.

2. ☒ The filing fee is calculated below:

CALCULATION OF FEES								
ITEM		TOTAL NO. OF CLAIMS		NO. OF CLAIMS OVER BASE	LG/SM $ ENTITY FEE		$ AMOUNT	$ FEE
A	TOTAL CLAIMS FEE	12	-20	0	LG=$18 SM=$9	$	0	
B	INDEPENDENT CLAIMS FEE*	2	-3	0	LG=$80 SM=$40	$0	0	
C	SUBTOTAL - ADDITIONAL CLAIMS FEE (ADD FINAL COLUMN IN LINES A + B)							$ 0
D	MULTIPLE-DEPENDENT CLAIMS FEE				LARGE ENTITY FEE = $270 SMALL ENTITY FEE = $135			$ 0
E	BASIC FEE				LARGE ENTITY FEE = $710 SMALL ENTITY FEE = $355			$ 355 00
F	TOTAL FILING FEE (ADD TOTALS FOR LINES C, D, AND E)							$ 0
	*LIST INDEPENDENT CLAIMS 46,52							

3. ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Account No. 50-1314. A copy of this sheet is enclosed.

4. ☒ A check in the amount of $ 355 is enclosed.

5. ☒ Cancel in this application original claim(s) 2-45 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

6. ☒ Amend the specification by inserting before the first line the sentence:

This is a ☒ continuation of application Serial No. 09/130,542 filed August 6, 1998, which application is hereby incorporated by reference in its entirety.

7a. ☐ New formal drawings are enclosed.

7b. ☐ Priority of application Serial Nos.:

[COUNTRY] application Serial No. [APPL'N #] filed [FILING DATE] is claimed under 35 U.S.C. § 119.

7c. ☐ The certified copy of the priority application was filed in prior application Serial No. [APPL'N #], filed [FILING DATE].

8. ☒ The prior application is assigned of record to: NDT, Inc.

9. ☒ The power of attorney in the prior application is as listed on the attached copy of the declaration filed in the patent application.

a. ☐ The power appears in the original papers in the prior application.

b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. ☒ Address all future communications to:

Stefan J. Kirchanski
HOGAN & HARTSON L.L.P.
Biltmore Tower
500 South Grand Avenue, Suite 1900
Los Angeles, CA 90071
Telephone: (213) 337-6700
Facsimile: (213) 337-6701

10a. ☒ A preliminary amendment is enclosed. (Claims added by this amendment have been properly numbered consecutively beginning with the number next following the highest numbered original claim in the prior application.)

10b. ☐ A separate check for $___ is enclosed to cover additional claims added by the preliminary amendment.

11. ☒ Enclosed find the following declaration(s) in support of Small Entity status for this application:

- ☒ Inventor(s)
- ☒ Individual other than inventor
- ☐ Nonprofit organization
- ☐ Small business concern

12. ☒ The statement(s) of Small Entity Status filed in the prior application is (are) still proper.

13. ☒ Other enclosure: Notice of Change of Attorney Address and Associate Power of Attorney.

Date: November 13, 2000

Stefan J. Kirchanski
Registration No. 36,568

HOGAN & HARTSON L.L.P.
Biltmore Tower
500 South Grand Avenue, Suite 1900
Los Angeles, CA 90071
Telephone: (213) 337-6700
Facsimile: (213) 337-6701

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27 (b)) - INDEPENDENT INVENTOR

Docket No. 40178.2

Serial No.	Filing Date	Patent No.	Issue Date
unknown	herewith		

Applicant/ Patentee: **Chris De Bruijn et al.**

Invention: **CONTACT LENS AND OPHTHALMIC SOLUTIONS**

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled above and described in:

- ☒ the specification to be filed herewith.
- ☐ the application identified above.
- ☐ the patent identified above.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

- ☐ No such person, concern or organization exists.
- ☒ Each such person, concern or organization is listed below.

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities (37 CFR 1.27)

FULL NAME **NDT, Inc.**
ADDRESS **30100 Town Center Drive, Suite O-290, Laguna Niguel, CA 92677-5402**

☐ Individual ☒ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF INVENTOR **Chris De Bruijn**
SIGNATURE OF INVENTOR _____ DATE: 07.11.98

NAME OF INVENTOR **F. Richard Christ**
SIGNATURE OF INVENTOR _____ DATE: July 16, 1998.

NAME OF INVENTOR **Anthony J. Dziabo**
SIGNATURE OF INVENTOR _____ DATE: 11 Jul 98

NAME OF INVENTOR **Joseph Vigh**
SIGNATURE OF INVENTOR _____ DATE: July 21, 1998

NAME OF INVENTOR _____
SIGNATURE OF INVENTOR _____ DATE: _____

NAME OF INVENTOR _____
SIGNATURE OF INVENTOR _____ DATE: _____

NAME OF INVENTOR _____
SIGNATURE OF INVENTOR _____ DATE: _____

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SIGNATURE OF INVENTOR _____ DATE: _____

NAME OF INVENTOR _____
SIGNATURE OF INVENTOR _____ DATE: _____

PATENT
Docket No. 82419.0003
Express Mail Label No. EL589806672US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Art Unit: not assigned
Chris De BRUIJN et al.	Examiner: not assigned
Serial No: not known	
Filed: 13-Nov-00	
For: CONTACT LENS AND OPHTHALMIC SOLUTIONS	

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination on the merits please enter the following Preliminary Amendment into the ac0companying continuation application.

IN THE CLAIMS:

Please cancel Claim 1 without prejudice.

Please add the following new Claims 46-57:

46. A hydrogen peroxide-free ophthalmic solution comprised of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

47. The ophthalmic solution of Claim 46 further comprising a viscosity altering agent.

48. The ophthalmic solution of Claim 46 further comprising a sequestering agent.

49. The ophthalmic solution of Claim 46 further comprising a wetting agent.

50. The ophthalmic solution of Claim 49, wherein the wetting agent comprising a saponin.

51. The ophthalmic solution of Claim 46 further comprising an osmotic agent.

52. A contact lens solution containing a microbicidal concentration of of a naturally occurring microbicidal compound selected from the group consisting of berberine and hydrastine.

53. The contact lens solution of Claim 52 further comprising a viscosity altering agent.

54. The contact lens solution of Claim 52 further comprising a sequestering agent.

55. The contact lens solution of Claim 52 further comprising a wetting agent.

56. The contact lens solution of Claim 55, wherein the wetting agent comprises a saponin.

57. The contact lens solution of Claim 52 further comprising an osmotic agent.

REMARKS

It is respectfully submitted that the instant application is in condition for allowance and Applicants earnestly request notification of the same. If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 50-1314.

Respectfully submitted,

HOGAN & HARTSON L.L.P.

Date: 13-Nov-00

By: Stefan J. Kirchanski

Stefan J. Kirchanski
Registration No. 36,568
Attorney for Applicants

Biltmore Tower
500 South Grand Avenue, Suite 1900
Los Angeles, CA 90071
Telephone: (213) 337-6700
Facsimile: (213) 337-6701

PATENT APPLICATION

40178.2

Contact Lens and Ophthalmic Solutions

Chris De Bruijn
F. Richard Christ
Anthony J. Dziabo
Joseph Vigh

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to contact lens and ophthalmic solutions and in particular relates to methods to disinfect and clean soft and rigid gas permeable (RGP) contact lenses, effectively and safely while maintaining convenience and comfort for the contact lens wearer.

By "effectively" we mean that the levels of specified pathogenic micro-organisms as well as other contaminants such as proteins, lipids, etc., are removed or reduced by a prescribed amount within the period of time contact lenses are kept in their storage case and storage solution. This is commonly taken to be "overnight" which is estimated as 6 hours. By "safely" we mean that the prescribed reduction in pathogen and other contaminant levels is accomplished without concomitant damage to the tissues of the human eye and without deleterious alteration of the contact lens itself. By "convenience" we mean that the contact lens care solution will be such that a minimum number of steps will be required to render the contact lenses clean and disinfected and the complete compliance of the wearer to the prescribed contact lens care procedures will be more likely. By "comfort" we mean that the eyes of the wearer will be able to tolerate the direct instillation of the solution.

DESCRIPTION OF RELATED ART

Currently available contact lenses are made of hydrogels causing them to be soft so that they can be comfortably worn. Previously, contact lenses were either hard plastic (PMMA) or RGP and required the contact lens wearing patient to adjust to the

uncomfortable sensation of a foreign body in the eye. The advent of soft contact lenses has resulted in an increased adoption of contact lenses by the general population.

Contact lenses are commonly worn on a daily basis and kept in a storage case/solution during the night hours or whenever they are not being worn. During the wear and normal handling of contact lenses, microorganisms as well as biomolecules such as lipids, proteins, etc. can become adhered to the contact lenses and thus transferred to the storage case/solution. Furthermore, a tear film that contains proteins, lipids, and even microorganisms, which represent the natural flora of the ocular surface, covers the surface of the eye. Any of these components found in the tear film or on the external surface of the eye or the surrounding skin can be carried into the storage case/solution on the contact lens.

Some of the microorganisms that may be transferred from the eye or fingers to the storage case/solution may multiply therein and may later be pathogenic to the human cornea or other ocular structures. When the contact lens is returned to the eye following its overnight soaking period, it is possible for these pathogens to be applied to the surface of the eye. Although human tears contain natural anti-microbial agents, a pathogen-bearing lens in contact with the cornea of the eye can serve as a reservoir of infection that might overcome the eye's natural defenses. This is especially the case for soft contact lens as the material tends to uptake the microorganisms. The result of microbial growth—bacterial, protozoan or even fungal—can cause damage to the eye resulting in impaired vision and even blindness. Therefore, contact lenses should be daily disinfected to eliminate pathogenic organisms, usually overnight, i.e., six to eight hours, to protect the wearer's eyes from infection.

As has been stated earlier, it is also possible that other materials of biological origin can be transferred to the contact lens during wear and upon handling and transfer

between the eye and the storage case/solution. These materials include cellular debris, proteins, lipids, and inorganic ions such as those of calcium and magnesium. Such materials can adsorb to the surface or become embed in the sub-surface matrix of the soft contact lens often creating persistent deposits that can cause irritation by abrasion against ocular tissues, e.g., cornea and inner surfaces of the eye lids. Furthermore, these deposits can become sufficiently severe to significantly reduce the transparency of the contact lens perhaps leading to impairment of the optical performance of the contact lens. It is therefore of interest to prevent the deposition of or to break up any aggregations of these contaminating molecules during the period of overnight immersion of the contact lenses in the storage case/solution.

Various solutions have been developed over the years to ensure that contact lenses are essentially pathogen and deposit free and can be safely and comfortably worn following overnight storage. These contact lens solutions typically include anti-microbial substances as well as cleaning (active against both lipids and proteins), wetting and other agents for the disinfection and cleaning of contact lenses during storage after wear. These solutions generally have sufficient microbicidal activity that the numbers of potentially pathogenic microorganisms are reduced to a prescribed level during the overnight soaking period.

Disinfection agents typically used for other applications such as hard surface disinfection, instrument disinfection, topical skin disinfection, etc. are not necessarily applicable to contact lens and ophthalmic solutions. The high concentration used and aggressive nature of many of these agents are unsuitable for use with contact lenses due to interaction or damage to the lens or irritation to ocular tissue. "Strong" disinfecting agents are compounds such as thimerasol, chlorhexidine, hydrogen peroxide, and benzalkonium chloride. For example, three (3%) percent hydrogen peroxide instilled

directly in the eye or a lens soaked in hydrogen peroxide and applied to the eye will result in pain and severe irritation.

In the case of hydrogen peroxide, prior art answers to the problem of irritation are disclosed in U.S. Patents 3,912,451, 4,585,488, 5,145,644 and 5,7666,931. These references show various methods and chemistries wherein the disinfecting period is followed by a neutralizing step using catalase, an enzyme that catalyzes the breakdown of hydrogen peroxide to water. This approach has found some level of acceptance among contact lens wearers. However, acceptance has remained limited, because of the multiple steps of disinfection, neutralization, and rinsing are not convenient to the wearer. More importantly, the potential exists for the neutralization and rinsing steps to be completed incorrectly (non-compliance) leading to the potential for some residual hydrogen peroxide to come in contact with the surface of the eye with the onset of severe stinging and irritation.

More recently, so-called multipurpose solutions (MPS) with chemical disinfection agents, as disclosed in U.S. Patents 4,407,791, 4,525,346, 4,758,595, 4,820,352, 4,836,956, 5,422,073, 5,560,186, 5,593,637, and 5,756,045, have largely supplanted hydrogen peroxide systems in the marketplace because they are far more convenient than the hydrogen peroxide systems. In this case the wearer need only purchase and use a single solution leading to advantages in cost and convenience. The challenge of disinfection and cleaning without harm to the eye or the lens is particularly acute with the MPS products, however, since all of the various activities, e.g., wetting, contaminant dispersion, and disinfection, are required to co-exist in a single solution without antagonistic effects of one component on the activity of another. Furthermore, because the MPS can be instilled directly into the eye, the active anti-microbial component of these solutions must provide the required degree of pathogen reduction while being free of irritating or damaging sequelae to the surface and the anterior

segment of the eye or to the contact lens itself. There is no opportunity with an MPS to neutralize or rinse away the anti-microbial agent prior to applying the contact lens to the eye.

Generally therefore the art has found it difficult to formulate these MPS solutions to satisfy the following performance criteria. The successful solution must:

1. Show anti-microbial activity to reduce the numbers of common pathogens found on contact lenses to prescribed levels;

2. Show an ability to retard the deposition processes of proteins, lipids, and other materials onto or into the lens and to remove such deposits if they have formed;

3. Be nonirritating to the eye without the help of rinsing and/or neutralizing solutions;

4. . Be free of toxic metals or compounds and sensitizing agents so that no long term allergic or toxic response is provoked;

5. . Not adversely accumulate within or on the lens or adversely alter the wettability or the parameters (i.e., size, shape, and optical properties) of the lens or be released in amounts toxic to the eye during lens wear;

6. . Show adequate shelf-life (e.g. chemical stability);

7. Compatible with enzymes and other agents used in artificial tears or similar accessories to contact lens wear.

A prior art alternative to the use of chemical disinfecting agents are phenolic compounds (e.g., bioflavonoids) as disclosed in De Bruijn International Application

PCT/NL97/00092 and Dutch patent NL-1002484. Natural plant derived substances; such as bioflavonoids, can be employed in contact lens care products as natural disinfecting or preserving agents. While the use of bioflavonoids is desirable because they are natural plant products, the majority of bioflavonoids are complex combinations that are difficult to obtain, reproduce and assay.

As background, the method for evaluating the effectiveness of a disinfectant generally requires measuring the ability of the agent to reduce the numbers of viable organisms during a period of time consistent with the normal period of storage of contact lenses between wearings such as six to eight hours, i.e., "overnight". This reduction of numbers of organisms is typically reported in terms of the change in the common log of the microbial population as a result of exposure to the anti-microbial agent. For example, if the agent has effected a reduction in the concentration of a particular organisms in a challenge solution from 10^6 colony forming units (cfu) per milliliter (ml) to 10^2 cfu/ml within six hours of exposure then the change, or "log reduction", of the organism as a result of exposure to the agent would be 4.0 (logs). In other words, the number of viable organisms have been reduced to one ten-thousandth of the original level.

In procedures for verifying the effectiveness of contact lens disinfectants generally recognized guidelines call for the use of *Candida albicans* (a yeast), *Fusarium solani* (a mold), *Pseudomonas aeruginosa* (a Gram-negative bacterium), *Staphylococcus aureus* (a Gram-positive bacerium), *and Serratia marcescens* (a Gram-negative bacterium). It is generally accepted in the field of ophthalmic and contact lens solutions that an effective disinfectant will cause at least a three log reduction of each of the bacterial species and a

one log reduction of each of the yeast and mold within the storage time advocated for the contact lens care system, typically six to eight hours, i.e., "overnight".

These tests are most often performed by challenging the solution with a concentrated inoculum (e.g., 10^5-10^6 cfu/ml) of each test organism. Over time samples are taken and plated on a growth medium to estimate the number of live organisms remaining at each time point. Of particular interest is the six-hour time point that represents the duration of typical overnight storage of soft contact lenses. It should be apparent that such a challenge represents a worst case scenario since a far greater number of microbes is added than would ever be expected on a contact lens. Further, it should also be apparent that the results of the test may be significantly influenced by other components of the solution besides the disinfectant agent.

In the case of contact lens and ophthalmic solutions various agents are added to enhance compatibility with the eye. To avoid stinging or irritation it is important that the solution possess a tonicity and pH within the physiological range, e.g., 200-350 mOsmole for tonicity and 6.5-8.5 for pH. To this end, various buffering and osmotic agents are often added. The simplest osmotic agent is sodium chloride since this is a major solute in human tears. In addition propylene glycol, lactulose, trehalose, sorbitol, mannitol or other osmotic agents may also be added to replace some or all of the sodium chloride. Also, various buffer systems such as citrate, phosphate (appropriate mixtures of Na_2HPO_4, NaH_2PO_4, and KH_2PO_4), borate (boric acid, sodium borate, potassium tetraborate, potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS,

imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5.

Various viscosity building agents such as polyethylene glycol, surfactants, polyvinylpyrrolidone, polyvinyl alcohol, carboxymethyl cellulose and similar materials may be added to adjust the "body" and "feel" of the solution. Surface active agents, such as polysorbates, polyoxyethylenes and certain phosphonates may be added to ensure proper wetting and/or cleaning. Sequestering agents such as ethylenediaminetetraacetic acid (EDTA), phosphonates, citrate, gluconate and tartarate are also common additives for preservatives of, disinfection or cleaning solutions.

To date, the significant challenge in the development of ophthalmic and contact lens solutions, particularly the MPS solutions, has been to find disinfection agents with sufficient anti-microbial activity that are not at the same time damaging to the eye or contact lens. Due to the complex requirements to keep soft, hydrogel contact lenses clean, free of pathogen microbes, and comfortable to wear without damaging or changing the lens polymer or dimensional parameters and without any harm or side effects to the human eye, only very few compounds or systems have been qualified as suitable ophthalmic or contact lens solutions. It is therefore the object of the present invention to provide a solution that combines the use of a chemical agent (BDT) and natural ingredients with the strength of harsh chemical agents such as hydrogen peroxide while avoiding irritation or damage to the eye.

SUMMARY OF THE INVENTION

The present invention concerns the unexpected discovery that the disinfectant compound, BDT (**B**enzyl**D**imethyl-[2-[2-[(p-1,1,3,3 **T**etramethyl butyl) phenoxy)ethoxy]ethyl] ammonium chloride), which has been widely tested and used in hospital surface disinfection, topical pharmaceutical preparations, and even as preservatives for injectables has unexpectedly proven highly effective in the disinfection of contact lenses without irritation to the external ocular surfaces or alteration of the parameters of the contact lens itself. Further, it has been discovered that BDT is stable in aqueous solution and can coexist in an formulation with the variety of cleaning, tonicity, and comfort additives common to ophthalmic and contact lens solutions without an adverse effect on its activity. Finally, it has also been discovered that the effectiveness of ophthalmic solutions containing BDT can be successfully enhanced by the addition of naturally occurring plant products.

The basic active ingredient formulation of the present invention comprises an effective concentration of BDT (preferably 1 to 100 parts per million), either alone or with other additives, in an isotonic or nearly isotonic diluent buffered with an acceptable buffer to the physiologically natural range.

It has been discovered that a variety of discrete, isolated and well-characterized natural plant compounds show anti-microbial and cleaning activity. It has also been discovered that some of these anti-microbial compounds act in a synergistic and or complementary manner with other anti-microbial compounds, such as BDT, and thus enhances their anti-microbial action. The potential range of these anti-microbial compounds includes glycosides, alkaloids, phenolics (anthocyanins, quinones, flavonols

and flavonoids, etc.), and terpenoids (including phytosterols and carotenoids). Of particular interest are the following anti-microbial compounds; Allicin, Aucubin, Berberine, Bilberry extract, Caffeic Acid, Chlorogenic Acid, Echinacea extract, Ferulic Acid, Hydrastine, Lipoic Acid, Naringin, Oleuropein, Proanthocyanidins, Quercetin, and Rutin as stand alone disinfection agents or in combination with other anti-microbial agents.

Further, it has been discovered that saponins, can be used as a natural plant surface active or cleaning agents in lens solutions. Specifically triterpenoid saponins and steriod saponins are particularly effective in contact lens or ophthalmic solutions. Also, a wide range of other comfort and cleaning enhancers can be added to the basic solution without adverse affects on the activity of these natural compounds or combinations. Suitable additives include, but are not limited to, various wetting, buffering, osmotic, sequestering, and comfort enhancing agents can be added to enhance the final formulation. .

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following description is provided to enable any person skilled in the art to make and use the invention and sets forth the best modes contemplated by the inventors of carrying out their invention. Various modifications, however, will remain readily apparent to those skilled in the art, since the general principles of the present invention have been defined herein, specifically to provide an improved contact lens care solution.

The following examples will be employed to demonstrate the effectiveness of BDT as well as its compatibility and being complementary with other desirable additives. In progressing through these examples one can understand the "building blocks" of the preferred embodiment of contact lens and ophthalmic solutions incorporating BDT.

Example 1

Initial tests of BDT were made in a contact lens disinfectant solution containing a sodium phosphate buffer system (0.1% anhydrous monobasic sodium phosphate and 0.4% anhydrous dibasic sodium phosphate) made isotonic with sodium chloride (0.7%) and also including Pluronic F127 (0.2%), a polyoxyethylene. Various concentrations of BDT in these vehicles were tested for anti-microbial activity against three of the five organisms that make up the commonly accepted disinfection test panel. The "log reduction" data at six hours after challenge are shown in Table 1. "Log reduction" is the format of data presentation in all of the examples that follow. From these and additional similar experiments it has been observed that increasing concentration of BDT results in increasing kill of a wide range of microbes in six hours or less.

Table 1: Effect of BDT Concentration on Microbial Kill

	15 ppm BDT	**25 ppm BDT**
S. aureus	1.7	>5.0
P. aeruginosa	1.8	3.4
C. albicans	0.3	1.4

Example 2

Experiments with a variety of different buffering agents discovered interactions between BDT and the buffer. In particular , a borate-based formula (0.3% boric acid, 0.4% sodium borate, 0.4% sodium chloride and 0.2% Pluronic F127) produced a wider spectrum of microorganism kill than the comparable phosphate-based solution. Especially noteworthy is the enhanced kill of fungus (*Candida albicans*) effected by the use of the borate buffer.

Table 2: Comparison of Anti-microbial Activity of BDT in Borate vs. Phosphate Buffer

	25 ppm BDT Borate	25 ppm BDT Phosphate
S. aureus	>5.0	>5.0
P. aeruginosa	>5.0	3.4
C. albicans	4.3	1.4

Example 3

A wide variety of naturally occurring compounds shows anti-microbial activity. In Table 3a results are shown for the enhancement of the kill of *Pseudomonas aeruginosa* using Chlorogenic Acid and Berberine in a phosphate buffered solution with 25 ppm BDT.

Table 3a: Enhancement of *Pseudomonas* kill with Chlorogenic Acid or Berberine

	25 ppm BDT	25 ppm BDT 500 ppm Chlorogenic Acid	25 ppm BDT 100 ppm Berberine
P. aeruginosa	3.4	4.5	>5.0

In Table 3b Caffeic Acid, combined with BDT in the presence of borate buffer, 250 ppm Chlorogenic Acid, and 0.2% Glycerin, improves the kill of *Pseudomonas aeruginosa* while maintaining the excellent log reductions for *Staphylococcus aureus* and *Candida albicans.*

Table 3b: Anti-microbial Enhancement of Caffeic Acid to BDT/Chlorogenic Acid

	25 ppm BDT/250 ppm Chlorogenic Acid	25 ppm BDT/250 ppm Chlorogenic Acid/ 1000 ppm Caffeic Acid

P. aeruginosa	2.8	>5.0
S. aureus	>5.0	>5.0
C. albicans	>5.0	3.8

Example 4

Table 4 shows the effect of adding 0.2% Glycerin to 25 ppm BDT and 250 ppm chlorogenic acid with borate buffer. In terms of microbiological disinfection this solution is very effective. The addition of Glycerin, a naturally occurring compound has essentially no effect on the disinfectant properties. There is evidence that Glycerin can reduce any minor toxic effects that a disinfectant agent might have on mammalian cells.

Table 4: Effect of the Addition of Glycerin on Anti-Microbial Activity

	25 ppm BDT 250 ppm Chlorogenic Acid 0.2% Glycerin	**25 ppm BDT 250 ppm Chlorogenic Acid**
S. aureus	>5.0	>5.0
P. aeruginosa	3.9	4.4
C. albicans	3.8	4.0

Example 5

Table 5 shows the effect of adding 0.2% Decanedioic Acid and 0.2% Glycerin to a formulation consisting of 25 ppm BDT and 1000 ppm Caffeic Acid in Borate Buffer. Decanedioic Acid is believed to improve the ocular comfort of contact lens solutions. As show in Table 5, there is no negative impact on anti-microbial activity with both Glycerin and Decanedioic Acid.

Table 5: Effect of the Addition of Glycerin + Decanedioic Acid on Anti-Microbial Activity

	25 ppm BDT 1000 ppm Caffeic Acid	25 ppm BDT 1000 ppm Caffeic Acid 0.2% Glycerin 0.2% Decanedioic Acid
S. aureus	>5.0	>5.0
P. aeruginosa	>5.0	>5.0
C. albicans	3.3	>5.0

Example 6

When the solutions were tested on animals, there was no observed toxicity or irritation when the materials were used in a "normal wear" cycle. That is, an isotonic BDT solution at physiological pH was tested on rabbits using Wohlk Weflex lenses. The lenses were disinfected in the test solution or in a control solution overnight. The lenses were then applied to the animals and worn by the animals for 8 hours of every 24 hours. This cycle was repeated for 21 days with no signs of irritation or toxicity. A second study used SUREVUE™ contact lenses. The lenses were soaked in the test solutions for 12 hours and then applied to the eyes of animals for a 12 hour wear cycle. Then a freshly soaked lens was substituted. This exaggerated wear test was on for 14 days of continuous wear of the test period. At the end examination of the animal eyes showed no signs of irritation or toxicity. Equivalent results were noted for the control solution, which was a commercially marketed MPS.

Example 7

A clinical study was conducted over a three month period with seven patients wearing SUREVUE™ (n=6) and Medalist™ (n=1) contact lenses. Patients received new lenses at the beginning of the study. The lenses were soaked overnight in an isotonic BDT test solution at physiological pH and rinsed in saline prior to wear. After 21 days there were no significant slit lamp findings, no irritation of the conjunctiva and no lens

deposits reported. No irritation or other negative findings were found during the tenure of the study.

Example 8

Table 8-a shows the anti-microbial activity of two naturally-occurring compounds, caffeic acid and chlorogenic acid, at 1000 ppm in borate-buffered saline. The borate-buffered saline alone was used as a control. It is evident that both naturally-occurring compounds have substantial anti-microbial activity against *Pseudomonas aeruginosa* within the six-hour challenge period. Either compound therefore may be useful as a preservative or disinfectant agent in a ophthalmic solutions.

Table 8-a: Anti-Microbial Activity of Caffeic Acid and Chlorogenic Acid in Borate-Buffered Saline

	Borate-Buffered Saline	**1000 ppm Caffeic Acid**	**1000 ppm Chlorogenic Acid**
S. aureus	0	0.7	0.4
P. aeruginosa	0	>5.0	2.2
C. albicans	0	0.2	0.1

Table 8-b shows the anti-microbial activity of a third naturally-occurring compound, berberine, at concentrations of 25 and 100 ppm in phosphate-buffered saline. It is evident that 100 ppm berberine has anti-microbial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* within the 6-hour challenge period. Berberine may therefore be useful as a preservative or disinfectant agent in a ophthalmic solutions.

Table 8-b: Anti-Microbial Activity of Berberine at Two Concentrations in Phosphate-Buffered Saline

	25 ppm Berberine	100 ppm Berberine
S. aureus	0	1.5
P. aeruginosa	0.1	1.8
C. albicans	0	0

Many alterations and modifications may be made by those having ordinary skill in the art without departing from the spirit and scope of the present invention. The words used in this specification to describe the invention and its various embodiments are to be understood not only in the sense of their commonly defined meanings, but to include by special definition in this specification structure, material or acts beyond the scope of the commonly defined meanings. Thus if an element can be understood in the context of this specification as including more than one meaning, then its use in a claim must be understood as being generic to all possible meanings supported by the specification and by the word itself. The definitions of the words or elements of the following claims are, therefore, defined in this specification to include not only the combination of elements which are literally set forth, but all equivalent structure, material or acts for performing substantially the same function in substantially the same way to obtain substantially the same result.

CLAIMS

We claim:

1. A contact lens solution containing a microbicidal concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride.

2. The contact lens solution of Claim 1, wherein the concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride is between 1 and 100 parts per million.

3. The contact lens solution of Claim 1, further comprising a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

4. The contact lens solution of Claim 1, further comprising a osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, andpropylene glycol.

5. The contact lens solution of Claim 1, further comprising between 0.01% and 5.0% glycerin.

6. The contact lens solution of Claim 1 further comprising between 0.01% and 2.0% of decanedioic acid.

7. The contact lens solutions of Claim 1 further comprising between 10 and 2500 parts per million of allantoin.

8. The contact lens solution of Claim 1 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, and saponins.

9. The contact lens solution of Claim 1 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

10. The contact lens solution of Claim 1 further comprising a naturally-occurring compound as an additional microbicidal agent and selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

11. The contact lens solution of Claim 1 further comprising a viscosity altering agent.

12. The contact lens solution of Claim 11, wherein the viscosity altering agent is selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, cellulose polymers and mixtures thereof.

13. An ophthalmic solution comprised of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

14. The ophthalmic solution of Claim 13 further comprising a viscosity altering agent.

15. The ophthalmic solution of Claim 13 further comprising a sequestering agent.

16. The ophthalmic solution of Claim 13 further comprising a wetting agent.

17. The ophthalmic solution of Claim 13 further comprising an osmotic agent.

18. The ophthalmic solution of Claim 16, wherein the wetting agent comprising a saponin.

19. A contact lens solution comprising: between 1 and 100 parts per million Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride, between 10 and 10000 parts per million of a naturally-occurring plant product, and borate buffer.

20. The contact lens solution of Claim 19 further comprising an osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, and propylene glycol.

21. The contact lens solution of Claim 19 further comprising between .01% and 2.0% glycerin.

22. The contact lens solution of Claim 19 further comprising between 0.01% and 2.0% of decanedioic acid.

23. The contact lens solutions of Claim 19 further comprising between 10 and 2500 parts per million of allantoin.

24. The contact lens solution of Claim 19 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, and saponins.

25. The contact lens solution of Claim 19 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

26. The contact lens solution of Claim 19 wherein the naturally-occurring plant product is selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

27. The contact lens solution of Claim 19 further comprising a viscosity altering agent.

28. The contact lens solution of Claim 27, wherein the viscosity altering agent is selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, and cellulose polymer.

29. A contact lens solution comprising: between 10 and 50 parts per million Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride, between 100 and 2000 parts per million of caffeic acid and a borate buffer.

30. The contact lens solution of Claim 29 further comprising an osmotic agent selected from the group consisting of trehalose, mannitol, sorbitol, lactulose, sodium chloride, and propylene glycol.

31. The contact lens solution of Claim 29 further comprising between .01% and 2.0% glycerin.

32. The contact lens solution of Claim 29 further comprising between 0.01% and 2.0% of decanedioic acid.

33. The contact lens solutions of Claim 29 further comprising between 10 and 2500 parts per million of allantoin.

34. The contact lens solution of Claim 29 further comprising a wetting agent selected from the group consisting of polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and mixtures thereof;

35. The contact lens solution of Claim 29 further comprising a sequestering agent selected from the group consisting as ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate and tartarate.

36. The contact lens solution of Claim 29 further comprising a viscosity altering agent selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, and cellulose polymers.

37. An ophthalmic solution comprising between 0.01% and 2.5% saponins as a wetting agent.

38. An ophthalmic solution comprising a naturally-occurring microbicidal compound selected from the group consisting of berberine, caffeic acid, and chlorogenic acid, and a borate buffer.

39. A method for cleaning and disinfecting contact lenses comprising the steps of:

contacting a contact lens to be cleaned and disinfected with an aqueous solution of between 1 and 100 parts per million of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride;

leaving the lens in contact with said aqueous solution for a predetermined time; and

removing the lens from said solution and placing it onto a user's eye without rinsing.

40. The method of Claim 39, wherein said aqueous solution further comprises a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

41. The method of Claim 39, wherein said aqueous solution further comprises a naturally-occurring plant product as an additional microbicidal agent and selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine, lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

42. The method of Claim 39 wherein the contact lens is selected from the group consisting of rigid gas permeable contact lenses and soft contact lenses.

43. A method for cleaning and disinfecting contact lenses comprising the steps of:

contacting a contact lens to be cleaned and disinfected with an aqueous solution of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, berberine, bilberry extract, caffeic acid, chlorogenic acid, echinacea extract, ferulic acid, hydrastine,

lipoic acid, naringin, oleuropein, proanthocyanidins, quercetin, and rutin;

leaving the lens in contact with said aqueous solution for a predetermined time; and

removing the lens from said solution and placing it onto a user's eye without rinsing.

44. The method of Claim 43, wherein said aqueous solution further comprises a physiologically compatible buffer selected from the group consisting of phosphate, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, and Tricine.

~~44~~ 45. The method of Claim 43, wherein said aqueous solution further comprises between wherein the concentration of Benzyldimethyl {2-[2-(p-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl} ammonium chloride is between 1 and 100 parts per million.

46. The method of Claim 43 wherein the contact lens is selected from the group consisting of rigid gas permeable contact lenses and soft contact lenses.

ABSTRACT OF THE DISCLOSURE

Benzyldimethyl{2-[2-(p-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl} ammonium chloride (BDT) forms the basis of contact lens solutions that are unusually effective at reducing the number and wide variety of pathogenic microorganisms that may infect rigid gas permeable or soft contact lenses. Furthermore, it has been discovered that natural occurring compounds alone and in combination with chemical agents can be used in ophthalmic solutions such as contact lens solution to enhance and complement their anti-microbial, cleaning and wetting activity or to reduce irritation to the eye. The basic contact lens solution comprises an effective concentration of BDT (preferably 1 to 100 parts per million), with naturally occurring plant products possessing activities complementary to BDT, in an isotonic diluent buffered with a physiologically acceptable buffer to a physiologically natural range.

Docket No.
40178.2

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CONTACT LENS AND OPHTHALMIC SOLUTIONS

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Daniel L. Dawes, Registration No. 27123
Stefan J. Kirchanski, Registration No. 36568

Send Correspondence to: **Stefan J. Kirchanski**
Graham & James LLP
650 Town Center Drive, Sixth Floor
Costa Mesa, CA 92626-1925

Direct Telephone Calls to: *(name and telephone number)*
Stefan J. Kirchanski (714) 751-8800

Full name of sole or first inventor **Chris De Bruijn**
Sole or first inventor's signature — Date 9.11.98
Residence **Gartenstiege 25, 48683 Ahaus, Germany**
Citizenship
Post Office Address **Gartenstiege 25, 48683 Ahaus, Germany**

Full name of second inventor, if any **F. Richard Christ**
Second inventor's signature — Date F. Richard Christ — 7/16/98
Residence **650 Lombardy Lane, Laguna Beach, CA 92651**
Citizenship
Post Office Address **650 Lombardy Lane, Laguna Beach, CA 92651**

Full name of third inventor, if any
Anthony J. Dziabo

Third inventor's signature — Date
Anthony J Dziabo — 11 July 98

Residence
21241 Avenida Nubes, Lake Forest, CA 92630

Citizenship

Post Office Address
21241 Avenida Nubes, Lake Forest, CA 92630

Full name of fourth inventor, if any
Joseph Vigh

Fourth inventor's signature — Date
Joseph E Vigh — July 21, 1998

Residence
500 Fordham Drive, Placentia, CA 92670

Citizenship

Post Office Address
5000 Fordham Drive, Placentia, CA 92670

Full name of fifth inventor, if any

Fifth inventor's signature — Date

Residence

Citizenship

Post Office Address

Full name of sixth inventor, if any

Sixth inventor's signature — Date

Residence

Citizenship

Post Office Address